GARDP

Global Antibiotic Research & Development Partnership

GLOBAL CHALLENGES

SERIOUS BACTERIAL INFECTIONS

INFECTIONS ARE BECOMING MORE DIFFICULT TO TREAT

Serious bacterial infections (SBIs) are a major cause of death for people in hospitals and other healthcare settings, and one of the world's biggest killers, claiming 7.7 million lives each year.[1] SBIs are those caused by harmful bacteria which, if not treated promptly or appropriately, can go on to cause severe illness and potentially life-threatening complications, such as organ failure or sepsis. Over the last century, antibiotics have provided a means of protecting people from SBIs and in doing so have increased life expectancy by an incredible 23 years.[2]

However, in recent decades the rise and spread of drug-resistant infections has started to reverse that trend. This growing resistance to antibiotics, including those kept as a last resort (such as carbapenems), is already leaving clinicians with vanishingly few treatment options. But now, research suggests that this antimicrobial resistance (AMR) crisis has reached a critical tipping point. With mortality having remained relatively stable in recent decades, the number of AMR-related deaths is now expected to rise sharply, increasing by more than 70% globally by 2050.[3]

THE RISE AND SPREAD OF GRAM-NEGATIVE INFECTIONS

One reason for this sudden step change is the proliferation of multidrug-resistant Gram-negative bacteria, which are a leading cause of hospital-acquired infections. Often these pathogens have the ability to not only pass between people or via objects, but also form tough biofilms on hospital equipment, like ventilators and catheters. This can enable them to become entrenched in healthcare settings and make it difficult to prevent their spread. In addition to this, multidrug-resistant Gram-negative infections tend to be the most difficult to treat, and also pose greater challenges when it comes to developing new antibiotics.

Indeed, this and the steady withdrawal of the pharmaceutical industry from antibiotic research and development (R&D) in recent decades, has meant that the world has failed to keep up the pace of innovation needed to produce new antibiotics with activity against multidrug-resistant infections. As a result, Gram-negative infections are now able to spread with increasing ease and this is expected to fuel a sharp rise in SBIs, with Gram-negative infections making up a growing proportion of AMR-related deaths.

Much of this could be mitigated through the development of new antibiotics that target the most harmful Gram-negative bacteria, and by ensuring they reach the people who need them.[3] Global and national initiatives have been launched in recent years with the aim of stimulating a revival of the antibiotic pipeline, through the use of financial incentives. However, while such efforts may encourage industry to develop new antibiotics, by themselves they cannot guarantee that the antibiotics most needed will be developed or will reach the people that most need them.

As things stand, many people around the world with SBIs do not have access to the appropriate antibiotics that already exist, particularly in low- and middle-income countries (LMICs). Recent research by GARDP suggests that in some countries fewer than 1 in 15 people with a SBI caused by carbapenem-resistant bacteria are receiving the right treatment, because of a lack of access to antibiotics.

1. *GBD 2019 Antimicrobial Resistance Collaborators, 2022. Global mortality associated with 33 bacterial pathogens in 2019: a systematic analysis for the Global Burden of Disease Study 2019.*
2. *Hutchings, M., Truman, A.W. and Wilkinson, B. Antibiotics: past, present and future. Curr Opin Microbio. 2019 Oct:***51***:72-80*
3. *GBD 2021 Antimicrobial Resistance Collaborators. Global burden of bacterial antimicrobial resistance 1990–2021: a systematic analysis with forecasts to 2050. Lancet 2024;* **404***: 1199–226*

GARDP'S FOCUS ON THE MOST DIFFICULT TO TREAT INFECTIONS

The latest research suggests that if these challenges can be overcome, more than 11 million deaths could be prevented by 2050, through the development of new Gram-negative antibiotics, and a further 50 million, by improving access to essential antibiotics more broadly.[3] GARDP's unique public-private partnership model is designed to do precisely that. By prioritizing the public health impact, affordability and access within high-burden countries, our focus is on the development of antibiotic treatments that target World Health Organization (WHO) priority pathogens – multidrug-resistant infections that pose the greatest threat to public health – and ensuring that people in need have access to them.

Through GARDP's dedicated programme for SBIs, we are working with partners to accelerate the development of innovative new treatments that are effective against the most harmful multidrug-resistant Gram-negative bacteria. At the same time, GARDP is expanding access to new and existing treatments for SBIs, including those that can lead to sepsis in adults and children.

By partnering with Japanese pharmaceutical firm Shionogi, for example, GARDP is accelerating access to cefiderocol, an antibiotic approved for use in complicated urinary tract infections, hospital- and ventilator-associated pneumonia caused by Gram-negative bacteria in adults. As of 2021, cefiderocol is the only recently authorized antibiotic agent with activity against all three Gram-negative bacteria on the WHO critical priority pathogen list- *Acinetobacter baumannii, Pseudomonas aeruginosa, Klebsiella pneumoniae* and *Escherichia coli*.

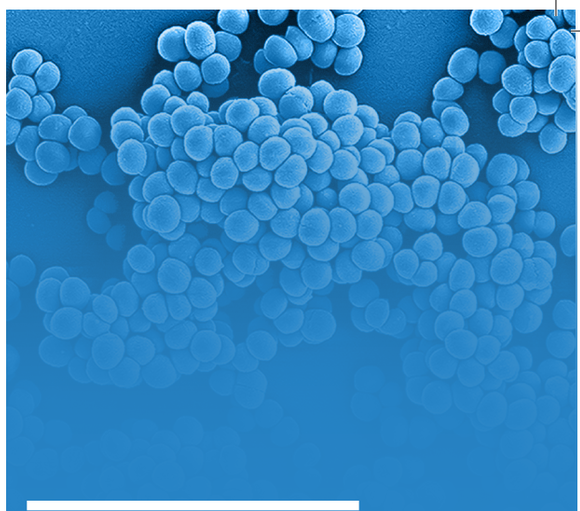
Through our innovative licensing agreements with Shionogi, and with support from the Clinton Health Access Initiative and Orchid Pharma, GARDP is expanding equitable and sustainable access to cefiderocol in 135 countries. At the same time, GARDP is working with Bugworks Research Inc. to co-develop a novel, broad-spectrum antibiotic called BWC0977 and make it accessible in 146 countries. In the laboratory, this candidate drug has demonstrated activity against multidrug-resistant bacteria that commonly cause life-threatening serious bacterial infections.

SEPSIS

SBIs can lead to life-threatening complications, such as sepsis. This can occur when an infection triggers an extreme response from the body's immune system, causing damage to tissues and resulting in multi-organ failure. Sepsis is one of the world's biggest killers and responsible for one in five deaths worldwide, with the majority of cases caused by SBIs. Drug resistance is also a major factor in determining clinical unresponsiveness to treatment and the rapid evolution to sepsis and septic shock.

Patients with sepsis due to infection with resistant pathogens have been found to have a higher risk of hospital mortality. This reinforces the need for timely effective antibiotics not only to prevent development of sepsis, but also for its clinical management. GARDP is working to reduce the threat posed by sepsis by developing and improving access to treatments that are effective against multidrug-resistant SBIs, including vulnerable populations, such as children, who make up roughly half all sepsis cases. Such efforts include the clinical and access development and commercialization of innovative new treatments, expanding and accelerating access to existing treatments, and evaluating the effectiveness of existing treatments when used in combination for children.

In addition to this, GARDP is exploring ways to repurpose old antibiotics for new use. This includes a project aimed at developing a new treatment regimen for sepsis caused by drug-resistant Enterobacterales, which includes a particularly difficult to treat group of bacteria called extended-spectrum beta-lactamase-producing Enterobacterales. These are a big problem and a major killer, particularly in LMICs. GARDP's approach would not only save lives, but would also deliver cost-effective alternative treatments to carbapenem antibiotics, while providing better outcomes for community-acquired sepsis.



WHO Bacterial Priority Pathogens List, 2024 update